Underrepresentation of vulnerable older patients with cancer in phase II and III oncology registration trials: a case-control study

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Abstract

Objectives
We aimed to determine the proportion of “fit” versus “vulnerable” older patients with cancer included in phase II and III oncology registration trials, as compared to the proportions in a real life oncology setting.

Methods
Trial and patient characteristics of older (≥70 years) patients treated at the OECI-designated clinical cancer centre in Kortrijk and included in a phase II or III oncology registration trial were collected retrospectively. These patients were matched individually with randomly-selected patients from the general oncology setting, based on gender, age, tumour type, tumour stage, and treatment intent. Patients’ fitness, based on routine Geriatric-8 (G8) screening, was retrieved from prospectively constructed databases.

Results
Between November 2012 and October 2018, 218 older patients with cancer were included in a phase II or III oncology registration trial. Of those, 41 cases with a mean age of 76,0 years were included in the analyses. A Fisher’s Exact Test revealed a statistical significant difference between cases and matched controls, with a higher proportion of “fit” patients included in phase II or III oncology registration trials compared to the proportion in the matched control group (respectively 70.7% and 41.5%, $p<0.010$).

Discussion
We provide evidence for the hypothesis that older patients included in phase II or III oncology trials are significantly fitter than the real life oncology population. Some form of geriatric evaluation should be integrated in future cancer clinical trials to enable stratification according to this parameter and allow subgroup analysis. This will broaden the application and interpretation of trial results.

1. Introduction

With the current demographic revolution, a result of the ageing of populations, epidemiologic data have predicted that the cancer incidence in older (≥ 65 years) adults will increase with 67% by 2030 in the United States.[1] Despite the continued increase in cancer incidence in older individuals, data from large cooperative groups have shown that only 22 to 32% of the older patient population participates in trials for cancer therapy.[2-4] However, the majority of older adults enrolled on clinical trials have a good Eastern Cooperative Oncology Group Performance Status (ECOG PS) which makes them not representative for the majority of patients seen in the clinic. The oncogeriatric population is very heterogeneous, and based on their general health status they can be categorized as "fit", "vulnerable", or "frail", which respectively corresponds to functionally independent patients, those with increased risk of developing dependency, and those who have a minimal functional reserve.[5-7]

Phase II and III registration trials are designed for the approval of new drug applications (NDA) or supplemental new drug applications (sNDA) for the extension of indications and/or posology. As the inclusion and exclusion criteria are very strict, usually only fit older patients can be enrolled[8], limiting the applicability of evidence-based recommendations within the field of oncology to older patients with cancer who may have a vulnerable or frail profile.[9,10] In geriatric oncology, clinical judgement alone is not sufficient for optimal treatment planning. Before its initiation, oncologists must be aware of age-related changes and identify the subset of patients who are vulnerable and at risk of increased treatment toxicity in order to ensure effective and safe cancer treatment in this patient population.[11-13]

The National Comprehensive Cancer Network (NCCN), the International Society of Geriatric Oncology (SIOG) and the American Society of Clinical Oncology (ASCO) recommend a geriatric evaluation of all patients with cancer aged 65 years and older.[14-16] They suggest a two-step method consisting of a short screening tool to select patients who need further multidisciplinary evaluation to guide treatment-related decisions as well as to implement geriatric interventions.[14,17-20] In the General Hospital Groeninge, we opt for the Geriatric-8 (G8) as a first step screening tool to identify older patients with cancer who would benefit from a more in-depth evaluation. The latter, also referred to as a comprehensive geriatric assessment (CGA), represents the second step. The G8 alone, however, appears to be predictive for functional decline and overall survival.[21-23] Older adults with cancer, characterized as fit from this screening, are assumed to benefit from the same treatment as younger patients. If these patients could be separated from those that would not benefit or even have a detrimental effect of treatment, treatment side effects and survival loss could be decreased in the latter population. The CGA is a comprehensive measure to recognize heterogeneity among older adults and to characterize the "functional age" of an older patient, allowing individualized approaches for cancer treatment. Furthermore, it detects unsuspected conditions in more than 50% of patients older than 65 years that may affect their ability to complete cancer treatment.[24-26]

Over the past few years, Dr. Arti Hurria advocated for the accrual of (vulnerable) older patients with cancer in clinical trials to improve the evidence base for treatments in this growing population.[27-30] Her research topics related to older adults with cancer and the use of a geriatric assessment (GA) had a considerable influence on our research perspectives. The past years, many academic studies on the clinical relevance of a CGA were carried out by our research group.[31-34]

At present, no data have been published concerning the proportion of fit versus vulnerable/frail older patients with cancer included in a clinical trial in a general hospital setting, compared to the real life population of older patients with cancer. Therefore, our aim was to evaluate these proportions of G8-negative and G8-positive older patients with cancer recruited in phase II and III oncology registration trials.

2. Methods

2.1. Study population and design

Patients were recruited upon presentation at the Kortrijk Geriatric Oncology Clinic. The General Hospital Groeninge is a 1054-bed non-for-profit public-private partnership (PPP) teaching hospital. Eligible patients needed to be ≥70 years at the time of trial inclusion, be diagnosed with a histologically confirmed solid tumour or haematological malignancy (any stage and any type of treatment), be included in a phase II or III oncology registration trial at the Organisation of European Cancer Institutes (OECI)-designated clinical cancer centre of the General Hospital Groeninge, Kortrijk, Belgium, and have been evaluated with the G8 screening tool or full CGA. All geriatric data needed to be collected within six months from trial inclusion. Patients included in elderly-specific phase II or III oncology registration trials were excluded. The online Appendix A summarizes the phase II/III trials included in analysis and their characteristics.

Patients recruited in phase II or III oncology registration trials were named 'cases' and have been matched to older patients from the general oncology setting included in the oncogeriatric database from the General Hospital Groeninge, further referred to as 'matched controls'. Cases and controls were matched if they were equal on following five criteria: gender, age, tumour type, tumour stage, and treatment intent. The research associate (L.T.) was not informed about their G8 (and CGA) result. If there was no match available in the database that fulfilled the matching criteria, cases were excluded from analysis.

The hypothesis of this study was formulated prospectively. Ethical approval was obtained by the local ethics committee of the General Hospital Groeninge (AZGS2015023). Formerly, the ethics committee approved registration of demographic, oncology and geriatric parameters within the framework of the KPC_24_A_025 (AZGS2012057), PROACTIVE (AZGS2012061), and REGERCAN (AZGS2015081) trials. These data have been retrospectively analysed within the scope of this research and have been registered without written consent in the oncogeriatric database since G8 and/or CGA are routine practice at our hospital (online Appendix B: Care Model Geriatric Oncology General Hospital Groeninge). Between November 2012 and October 2018, a mean of 65.6% of oncogeriatric patients with diagnosis and treatment at our hospital have received a GA (minimum coverage of 39.4% , maximum coverage of 73.3%).

2.2. Measures

Three onco-psychologists (L.K., J.D.Z., E.M.) and two research associates (L.P., M.L.) were qualified to conduct the G8 and/or CGA and are called trained healthcare workers (THCWs). Since G8 screening data are available for all patients, we defined patients with a G8 score of more than 14 as G8-negative (G8-) or fit and those who scored 14 or less as G8-positive (G8+) or vulnerable.[18,22,23,35]

In case of a positive screening (G8 ≤14), a full CGA was conducted. The CGA examines different age-related domains including comorbidities (Charlson Comorbidity Index (CCI)[36]), polypharmacy (number of drugs), functional status (Activities of Daily Living (ADL), instrumental Activities of Daily Living (iADL)[37,38]), cognition (mini-mental status examination (MMSE) or Freund Clock Drawing Test (CDT)[39,40]), nutrition (Mini Nutritional Assessment - Short Form[41]), emotional status (Geriatric Depression scale – 15[42]) and physical status (number of falls). When one reaches the cut-off value of a certain CGA domain, this patient is suggested to be 'vulnerable' on that specific domain. Two

definitions of vulnerability based upon CGA result were used: vulnerability in one or more domains and vulnerability in two or more domains.[35,43]

2.3. Statistical analysis

Descriptive statistics were performed to present patient and trial characteristics. In order to assess the comparability of both cohorts, also demographic and clinical data were statistically analysed by using an independent sample t-test or Exact Pearson Chi-Square test. The proportions of G8- and G8+ patients were assessed by a 2x2 Contingency table to determine the association between the two variables condition (G8-/G8+) and group (case/matched control). A Fisher's Exact test was used to compare the proportions of G8+ patients in the group of cases, matched controls and older patients with cancer included in the oncogeriatric database at the General Hospital Groeninge. P-values below 0.05 were considered statistically significant. All statistical analyses were conducted using Microsoft Office Excel 2013 (Microsoft, Inc., Redmond, WA) and IBM SPSS v.24 (SPSS, Inc., Chicago, IL) software.

3. Results

3.1. Study population characteristics

From November 2012 till October 2018, 3,017 older patients with cancer were evaluated by a G8 screening and/or CGA in the Kortrijk Geriatric Oncology Clinic. Within the same period, 688 patients had been included in phase II or III oncology registration trials. Of those, 380 patients were excluded as they were not 70 years or older, and another 116 patients had a protocol-specific screen failure for the respective trials. Next, another 170 were excluded as the G8 was not assessed (N=122) or not within six months from trial inclusion (N=48), five were part of an elderly-specific trial, and for two patients no match was possible. The remaining 41 cases were eligible for analysis (**Fig. 1**). Of all 41 patients, 18 had a geriatric evaluation before trial inclusion (median time 22 days), 4 had an assessment on the moment of trial inclusion, and 19 had an evaluation after they were included in a phase II or III clinical trial (median time 89 days).

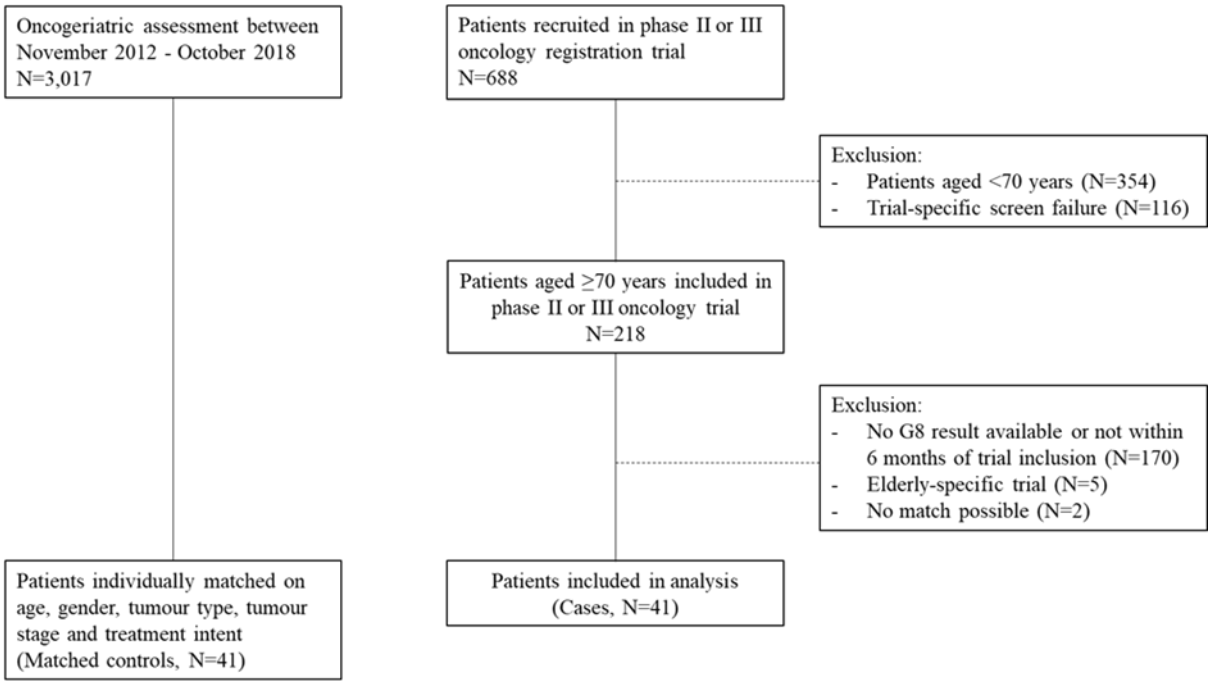

Fig. 1. Patient flow diagram.

Cases had an average age of 76.0 years and matched controls had an average of 75.0 years (range for both cohorts: 70-86 years). The selected cohorts included more male than female individuals (75.6% and 24.4%, respectively). Within the case cohort, more patients were married in comparison to the control group (80.5% and 68.3%, respectively), but the living situation was similar in both cohorts with ≥95.0% living at home. Professional homecare was used more by matched controls than by the cases (58.5% and 39%, respectively). Patients included in phase II or III oncology registration trials were diagnosed with the following malignant conditions: genitourinary (39.1%), haematological malignancies (34.1%), digestive tract (12.2%), gynaecological (9.7%), and breast (4.9%). Most tumours were advanced (51.2%) and a treatment with palliative intent was assigned to a majority of patients (58.5%). Full demographic and oncology characteristics of the cases and matched controls are presented in **Table 1**.

Table 1. Demographic and oncology characteristics of Cases and Matched controls

	No. of Cases	%	No. of Matched controls	%	Significance
Demographic characteristics					
Sex					
Male	31	75.6	31	75.6	*p = 1.00*
Female	10	24.4	10	24.4	
Age, y					
Mean (range)	76.0 (70-86)		75.0 (70-86)		*p = 0.98*
Education: age, y					
Mean (range)	17.1 (13.5-23)		16.9 (13-23)		*p = 0.76*
Marital Status					
Married	33	80.5	28	68.3	*p = 0.41**
Widow-er	6	14.6	5	12.2	
Divorced	1	2.4	3	7.3	
Single	1	2.4	4	9.8	
Alone	0	0.0	1	2.4	
Living situation					
Home with partner	32	78.0	27	65.9	*p = 0.71**
Home – alone	7	17.1	10	24.4	
Home – with family member	1	2.4	2	4.8	
Other	1	2.4	2	4.8	
Professional homecare					
Yes	16	39.0	24	58.5	*p = 0.08*
No	25	61.0	17	41.5	
Clinical characteristics					
Primary tumour diagnosis					
Breast	2	4.9	2	4.9	*p = 1.00**
Digestive	3	7.3	3	7.3	
Genitourinary – bladder	4	9.8	4	9.8	
Genitourinary – prostate	12	29.3	12	29.3	
Gynaecological – ovary and primary peritoneal carcinoma	2	4.9	2	4.9	
Gynaecological – corpus uteri	1	2.4	2	4.9	
Gynaecological – other	1	2.4	0	0.0	
Haematological – non-hodgkin lymphoma	11	26.8	11	26.8	
Haematological – chronic lymphocytic leukemia	3	7.3	3	7.3	
Diagnosis					
New diagnosis	20	48.8	24	58.5	*p = 0.62**
Progression	19	46.3	16	39.0	
Relapse	2	4.9	1	2.4	
Tumour type					
Early (I-II)	6	14.6	6	14.6	*p = 1.00*
Advanced (III-IV)	21	51.2	21	51.2	
Not reported	14	34.1	14	34.1	
Treatment intent					
Curative	16	39.0	16	39.0	*p = 1.00**
Palliative	24	58.5	24	58.5	
No active treatment/supportive care	1	2.4	1	2.4	

*The assumption for Chi-square Test that no more than 20% of the expected counts may be less than 5 and all individual expected counts must be 1 or greater, was not fulfilled for this analysis. Results were however reported to give an idea of the sampling distribution.

3.2. Trial characteristics

As illustrated in **table 2**, there were less phase II than phase III oncology registration trials included in this retrospective study (39.3% and 60.7%, respectively). Also, most of the trials were commercial (71.4%). The clinical specialty groups of the trials included in our analysis were genitourinary tumours (35.7%), haematological malignancies (32.1%), digestive oncology (14.3%), gynaecological malignancies (7.1%), and breast cancer (7.1%). Targeted therapy alone and in combination with

chemotherapy were the most common types of investigational therapy (35.7% and 17.9%, respectively). Targeted therapy included monoclonal antibodies (e.g. Rituximab), PARP inhibitors (e.g. niraparib), FGFR inhibitors (e.g. pemigatinib), tyrosine kinase inhibitors (e.g. ibrutinib), and CDK inhibitors (e.g. ribociclib). More information on the phase II/III oncology registration trials included in analysis can be found in the online Appendix A.

Table 2. Trial characteristics (N=28)

		N (%)
Type of trial	Phase II	11 (39.3)
	Phase III	17 (60.7)
	Academic	8 (28.6)
	Commercial	20 (71.4)
Clinical specialty group	Breast	2 (7.1)
	Digestive	4 (14.3)
	Genitourinary – bladder	2 (7.1)
	Genitourinary – prostate	8 (28.6)
	Gynaecological	2 (7.1)
	Haematological oncology	9 (32.1)
	Solid or haematological malignancies	1 (3.6)
Type of investigational therapy		
Combination of drugs	Chemotherapy and molecular targeted therapy	5 (17.9)
	Chemotherapy, radiotherapy, molecular targeted therapy	3 (10.7)
	Chemotherapy, radiotherapy, hormonal therapy	1 (3.6)
	Hormonal therapy and molecular targeted therapy	2 (7.1)
Hormonal therapy	Hormonal therapy alone	3 (10.7)
	Hormonal therapy, radiotherapy, surgery	1 (3.6)
Targeted therapy		10 (35.7)
Chemotherapy		1 (3.6)
Radiotherapy		1 (3.6)
Other		1 (3.6)

3.3. Comparison of the proportion of vulnerable older patients in phase II or III oncology registration trials compared to the proportion in the general oncology setting

As presented in **figure 2**, 29 cases and 17 matched control patients were categorized as G8- (70.7% and 41.5%, respectively) while 12 cases and 24 matched controls were judged as G8+ (29.3% and 58.5%, respectively). A contingency table was created to assess the association between the two variables, condition (G8-/G8+) and group (case/control). A two-tailed Fisher's Exact test indicated a significant difference between the proportions G8- and G8+ older patients with cancer in the case and matched control group ($p<0.05$), as well as between the proportions in the case group and oncogeriatric database ($p<0.001$).

The proportions of G8- and G8+ patients in the matched control group resembled the proportions of G8- (43.9%) and G8+ (56.1%) older patients with cancer who had a geriatric screening between November 2012 and October 2018 and were included in the database ($p=0.8744$).

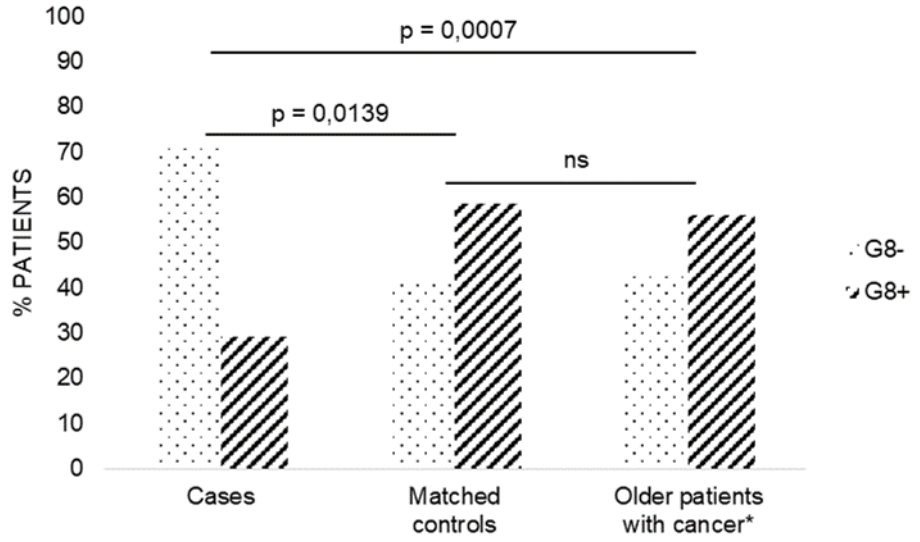

Fig. 2. Proportions of G8- and G8+ older patients with cancer in the group with cases, matched controls and patients included in the oncogeriatric database from the General Hospital Groeninge (*), determined by G8 score.

3.4. Determination of the CGA domains in which geriatric vulnerabilities are most frequently detected

Of all patients included, 29.3% of the cases (12/41) and 58.5% of the matched controls (24/41) had a positive G8 screening. Consequently, THCWs performed a CGA. Although not all CGA data were complete, abnormal test results of the G8+ patients in the groups of cases, matched controls and older patients with cancer included in the oncogeriatric database were most frequently detected in the domains of community functioning (58.3%, 75.0%, and 84.5%, respectively), nutrition (58.3%, 65.2%, and 72.6%, respectively), and polypharmacy (75.0%, 70.8%, and 69.7%, respectively). Based on the results of the CDT screening tool, G8+ cases showed a trend to score negative on the cognitive domain, in contrast to the control groups. However, all G8+ cases and matched controls scored negative on the MMSE (**Table 3**).

Table 3. CGA domains of G8+ Cases, Matched controls and the oncogeriatric population of the General Hospital Groeninge(*)

	Test	Range	Cut-off	No. of G8+ Cases (N=12**)	%	No. of G8+ Matched controls (N=24**)	%	No. of G8+ older patients with cancer* (N=1693**)	%
Functional status – self care	ADL	0-6	≤ 5	0/12	0.0	0/24	0.0	907/1668	54.4
Functional status – community functioning	iADL	0-8	≤ 7	7/12	58.3	18/24	75.0	1408/1666	84.5
Physical status	No. of falls	NA	≥1	3/12	25.0	5/23	21.7	594/1662	35.7
Cognition	MMSE	0-30	≤ 23	0/6	0.0	0/12	0.0	239/734	32.6
	CDT	0-7	≤ 4	0/5	0.0	5/13	38.5	233/804	29.0
Depression	GDS-15	0-15	≥ 6	2/10	20.0	2/20	10.0	230/1293	17.8
Nutrition	MNA-SF	0-14	≤ 11	7/12	58.3	15/23	65.2	1214/1673	72.6
Co-morbidities	CCI	0-37	≥ 4	2/12	16.7	0/24	0.0	453/1693	26.8
Polypharmacy	No. of drugs	NA	≥5	9/12	75.0	17/24	70.8	1180/1692	69.7

* patients included in the oncogeriatric database at the General Hospital Groeninge (November 2012 - October 2018)
** number of vulnerable patients included in the cohort (not all CGA domains were completed)

Abbreviations: ADL: Activities of Daily Living, iADL: instrumental Activities of Daily Living, MMSE: Mini Mental State Examination, CDT: Clock Drawing Test, GDS-15: 15-item Geriatric Depression Scale, MNA-SF: Mini Nutritional Assessment-Short Form, CCI: Charlson Comorbidity Index, NA: Not applicable.

The CGA conducted in G8+ patients enables the identification of vulnerable and frail profiles. In **table 4**, three categories within G8+ groups are displayed: vulnerable patients with a G8 score ≤14, those with a G8 score ≤14 and vulnerable in at least one domain of the CGA, and, last, patients with a G8 score ≤14 and vulnerability in at least two CGA domains. A two-tailed Fisher's Exact test revealed a significant difference between cases and matched controls for first two categories ($p<0.05$), but not for the last category ($p=0.064$). Still, the number of G8+ cases was significantly different from the older patients with cancer included in the oncogeriatric database for all three categories ($p<0.001$). There was no significant difference observed between the matched controls and the patients included in the oncogeriatric database ($p>0.05$).

Table 4. Identification of vulnerability by G8 and CGA in Cases, Matched controls and the oncogeriatric population of the General Hospital Groeninge(*)

Patient characteristics	Cases N=41 (%)	Matched controls N=41 (%)	Older patients with cancer* N=3017 (%)
G8 ≤14	12 (29.3%)	24 (58.5%)	1693 (56.1)
G8 ≤14 + 1 CGA domain 'vulnerable'	12 (29.3%)	24 (58.5%)	1685 (55.9)
G8 ≤14 + 2 CGA domains 'vulnerable'	10 (24.4%)	19 (46.3%)	1563 (51.8)

* patients included in the oncogeriatric database at the General Hospital Groeninge (November 2012 - October 2018)

4. Discussion

This paper aimed at identifying the proportion of G8+ older patients with cancer included in phase II/III oncology registration trials, compared to the proportion in a real life oncology setting. In this retrospective case-control study, at least 70% of older patients with cancer were designated fit by the G8 screening tool within six months from participation to a phase II or III oncology registration trial. This number is significantly different from the proportion of G8- older patients with cancer in the matched control group, as well as from the patients included in the oncogeriatric database. These data highlight the underrepresentation of vulnerable/frail older patients with cancer in phase II/III clinical trials.

The low recruitment of (vulnerable) older patients with cancer in clinical trials can be explained by strict eligibility criteria such as the ECOG PS and the exclusion of patients who are cognitively impaired.[2-4,44,45] Studies have revealed that most older patients with cancer would forgo a potentially life-saving treatment if it impacted function or cognition.[46,47] In our retrospective analysis, not all CGA data were complete and results on the cognitive domain should be interpreted cautiously as only half of the G8+ cases and G8+ matched controls fulfilled the CDT and MMSE. To allow a correct interpretation of table 3, absolute values of the number of G8+ cases, G8+ matched controls and G8+ older patients with cancer are indicated. Based on the results of the Freund CDT screening tool, the vulnerable patients included in phase II/III oncology registration trials seem to show a trend towards good cognitive functioning[9,48], especially in comparison with the matched controls and patients included in the oncogeriatric database. When participating to a clinical trial, more support is mandatory in case of reduced cognitive functioning as it is essential one understands the trial and therapy side effects. Also, the majority of patients included in this study were treated with palliative intent. If these patients with an already vulnerable or frail profile would be forced into a curative treatment setting, they might suffer from symptoms not only caused by cancer, but also by treatment-induced toxicity. This points out the lack of evidence-based data related to the benefits and risks of cancer treatment in the vulnerable older patient as mainly older patients with a fit profile are enrolled in clinical oncology trials.[49]

Indeed, the evidence base concerning the effectiveness of treatment and potentially adverse consequences among older and/or frail adults remains sparse. Adaptation of trial designs to allow more vulnerable patients to receive upfront dose reductions or less intense regimens could be a useful intervention as treatment prescriptions for older adults with cancer are largely based on evidence generated in younger or fitter older adults. Therefore, Hurria et al. suggested an extension of patent exclusivity and post approval evaluation to administer effective and safe curative cancer treatment for older adults with cancer.[50] In 2014, we introduced the concept of a dose-expansion cohort (DEC) dedicated in vulnerable older patients to be incorporated in phase 1b/2a protocols.[51] A DEC offers the opportunity to reassess the efficacy, toxicity and maximally tolerated dose in these patients in the early phases of drug development. This modification of clinical trials for older patients was seconded by Dr. Arti Hurria, who was in favour of adding a cohort of older patients with cancer to the treatment arm that was shown to be superior, in order to evaluate the tolerability in older adults.[28,52]

Another adaptation of trials concerns the standard end-points such as disease-free survival or response rate (respectively in curative/adjuvant and palliative setting). For older adults with cancer, these are less applicable as they often die from other causes than the disease itself or from relapse. As daily functioning could offer a more accurate illustration of treatment outcome, it is suggested to integrate CGA parameters as surrogate trial end-points for older adults. Evaluation of geriatric parameters could contribute to better understanding the impact of new therapies on older individuals with cancer and to improving care in this vulnerable population.[49,53] This case-control study advocates for the application

of a GA before treatment start as it offers a correct estimation of an older person's treatment tolerance and possible benefit.

In this study, we investigated in which CGA domains the two separate cohorts of G8+ cases and matched controls most often reached the assigned cut-off values. Community functioning (iADL), nutrition and polypharmacy appeared as most sensitive CGA domains. This outcome acknowledges previous literature pointing out iADL and nutritional status as strong individual prognostic factors for overall survival in patients with cancer.[18,54] Ideally, this outcome should be confirmed with a multicentre prospective cohort study.

To date, there is no consensus on a definition of frailty for oncology trials. Definitions in the general geriatric population are not specifically for older adults with cancer limiting their applicability. In this study, iADL, nutrition and polypharmacy were the CGA domains on which most G8+ patients reached the threshold, but it is plausible to consider other commonly applied criteria for the classification of patients as fit, vulnerable or frail. The EORTC Minimal Dataset interprets ≥1 dependency in G8, iADL, CCI, and Social Situation as vulnerability[20,49], while the NCCN older adult oncology guidelines judge elderly as vulnerable if they are ADL and/or iADL positive and as frail if they appear vulnerable on ADL, iADL, CCI, and/or physical, nutritional, affective, and cognitive domain.[14] For Droz et al. (2010), significant comorbidity, iADL dependence, and severe malnutrition are the criteria to judge one vulnerable or frail, depending on the grade of comorbidity.[55]

According to Hamaker et al. (2012), an older patient with cancer is considered vulnerable when impairment is detected in at least two CGA domains[35], while Soubeyran et al. (2011) used a less stringent definition as dependence in at least one domain is sufficient.[43] As indicated in **table 4**, there is only a small difference between older patients who are G8+ only and those who are G8+ and vulnerable in one or two CGA domains, and our conclusions remain the same regardless of the definition used. The easiest way to define vulnerability is a G8 score of 14 or less. In our hospital, THCWs conduct a full CGA in G8+ patients, or on specific request of the physician. Regarding the clinical significance of a CGA, the appropriate judgement of THCWs is crucial to identify vulnerable or frail patients. The number of positive CGA domains to define frailty remains undetermined in geriatric oncology. For future research, we will keep track of which domains could be decisive in order to define frailty.

Some considerations need to be made when interpreting these results. First, this case-control study was monocentric and only patients included in phase II or III clinical trials that took place in the General Hospital Groeninge were selected. Second, the analysed sample size is relatively small due to the (strong) inclusion and exclusion criteria and the retrospective nature of this study. Although G8 screening and CGA are routine practice at our cancer centre, not all data were complete or gathered within six months from trial inclusion. Additionally, we were unable to match two patients according to the five matching criteria (age, gender, tumour type, tumour stage and treatment intent). Third, the selection of phase II/III trials might not be a convenient representation for the oncology registration trials in a real life oncology setting. For example, breast cancer is far more frequent than gynaecological tumours, but in this case-control study, results showed the opposite. This can be explained by trials' availability to include patients and, again, the strict inclusion criterion of a G8 result available within six months from trial inclusion. At last, 75% of patients included in analysis were male. This underrepresentation of women in our analysis can be largely explained by the imbalance in trials. When six patients were confronted with breast or gynaecological malignant condition, there were twelve treated for prostate cancer, which does not correspond with demographic characteristics. Therefore, case-control matching was performed.

Some controls were conducted to confirm the generalizability of our results. First, the recent G8 result enables a correct estimation of trial patients' fitness which is decisive for the interpretation of study results. More importantly, based on five crucial parameters, cases have been matched to control patients included in the oncogeriatric database. This case-control matching corrects for any trial under- or overrepresentation and ensures a correct representation of the real life oncology population. Moreover, the proportions of G8- and G8+ older patients included in the matched control group resemble closely the proportions of older patients with cancer included in the oncogeriatric database, which suggests that the matched controls are representative for the older patients with cancer in a real life oncology setting. Furthermore, demographic and clinical characteristics of the excluded patients with CGA result available (N=48) have been analysed. An independent sample t-test and Exact Pearson Chi-Square test showed there was no statistically significant difference between the excluded patients and the cases, neither for the matching criteria gender (p=0.5), age (p=0.6), tumour type (p=0.1), tumour stage (p=0.5), and treatment intent (p=0.8), nor for the number of G8+ versus G8- cases (p=0.2) (data not shown). The majority of the excluded patients (56.1%) had a fit profile. However, this G8 result was obtained more than 6 months before or after trial inclusion, therefore no conclusions can be drawn.

To the best of our knowledge, we are the first to publish quantitative data on the proportion of vulnerable older patients with cancer included in clinical trials, in comparison to the real life population. We believe our data support the inclusion of G8 and/or CGA for oncogeriatric patients enrolled in clinical trials to improve adequate patient selection, risk stratification, and efficacy and safety evaluation. Agreement on a (more or less) uniform and straightforward evaluation of the fitness of the older population such as the G8 could contribute to better characterized patient populations, avoiding selection bias caused by the heterogeneity of the population.

In conclusion, this case-control study provides evidence for the hypothesis that older patients included in phase II or III oncology trials are significantly fitter than the real life oncology population. Integration of the G8 screening tool and/or CGA in future cancer clinical trials could enable stratification according to this parameter and allow subgroup analysis. New approaches to tackle the underrepresentation of vulnerable older patients with cancer in clinical trials are needed such as DECs in early phase trials and extra cohorts in later phase trials. This will broaden the application and interpretation of trial results.

Conflict of interest

The authors have no conflict of interest to declare.

Contributions

All authors have contributed substantially to the conception and design, acquisition of data and/or the analyses and interpretation of data, and manuscript writing. All authors have reviewed and approved this manuscript.

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